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DRAFT

Roche

Case ID **XB-1081**	Patient sex **Female**	Diagnosis **Her2-receptor negative breast cancer**	Tumor purity **49%**	Ordering physician **Dr. Ina Gomperts**
Patient MRN not specified	Patient DOB **09/19/1959**	Sample type **Tissue**	Sample collection date **09/29/2020**	Ordering institution **Institut für Onkologie**
Patient name not specified	Patient ethnicity not specified	Sample site **Breast**	Sample receipt date **10/05/2020**	Ordering institution ID not specified

Report summary

4 clinically significant variants & combinations
0 other biomarkers
2 relevant therapies
8 clinical trials

variant	present in combination	present in combination
BRCA1 p.E111fs	**ESR1** p.D538G	**PIK3CA** p.H1047R

variant

BRCA1 p.E111fs

VAF **6.9%** RD **1,727** Tier I-A

BRCA1 variants are often germline in nature with implications for treatment decisions and clinical management, and germline testing should be considered in the appropriate clinical context (NCCN, ESMO). Germline pathogenic mutations in BRCA1 are associated with hereditary breast cancer. Two PARP inhibitors are approved or recommended for certain HER2-negative breast cancer patients carrying germline pathogenic BRCA mutations (FDA, EMA, Health Canada, Swissmedic, TGA, NCCN, ESMO, eviQ). Clinical studies have reported survival benefit with PARP inhibitor treatment in patients with HER2-negative breast cancer carrying germline BRCA mutations, including patients with hormone receptor-positive and triple negative breast cancer. Subsequent analyses of these trials reported improved patient outcomes, but not improved overall survival. In a retrospective analysis, patients with either triple-receptor negative breast cancer or estrogen-receptor positive breast cancer harboring germline BRCA1/2 mutations experienced significantly higher pathological complete response rates as compared to patients without these mutations on neoadjuvant chemotherapy regimens. Patients with breast cancer harboring BRCA germline or somatic mutations match inclusion criteria for clinical trials.

Therapies approved/guidelines-recommended in: **Her2-receptor negative breast cancer**

- **olaparib**
- **talazoparib**

variant present in combination

ESR1 p.D538G VAF **50%** RD **1,750** Tier I-B

In a combined analysis of two phase III trials, patients with estrogen-receptor positive breast cancer harboring ESR1 mutations demonstrated worse progression-free survival and one-year overall survival on aromatase inhibitor therapy compared to estrogen inhibitor therapy. In a phase II trial, estrogen inhibitor therapy alone or in combination with PI3K inhibitor therapy showed no clinical benefit in patients with estrogen-receptor positive breast cancer harboring ESR1 mutations. In a phase I trial, patients with estrogen-receptor positive breast cancer harboring ESR1 mutations achieved partial responses on SERD therapy. Patients with estrogen-receptor positive/HER2-receptor negative breast cancer harboring ESR1 activating mutations match inclusion criteria for clinical trials, such as trials with selective estrogen receptor degraders. In a retrospective analysis of a phase III trial, estrogen-receptor positive breast cancer patients harboring ESR1 D538G demonstrated improved progression-free survival when treated with a combination of aromatase and MTOR inhibitors, versus aromatase inhibitor alone. In another clinical study, ESR1 D538G was associated with shorter overall survival and progression-free survival in breast cancer patients treated with aromatase inhibitors. In additional clinical studies, patients with estrogen-receptor positive breast cancer harboring ESR1 D538G progressed on aromatase inhibitors, estrogen receptor modulators and inhibitors and responded to anti-PD-1 antibody therapy. Preclinical studies suggest that ESR1 D328G is associated with resistance to estrogen receptor modulators in estrogen-receptor negative breast cancer cells in culture.

no approved therapies

2

combination

PIK3CA p.H1047R, **ESR1** p.D538G Tier II-C

In a clinical study, activating ESR1 mutations (D538G or Y537S) were associated with lack of clinical benefit in patients with HR+ breast cancer harboring PIK3CA activating mutations treated with a PIK3CA inhibitor in combination with an aromatase inhibitor. In a phase Ib clinical trial, one patient with estrogen-receptor positive breast cancer harboring ESR1 D538G and a PIK3CA mutation demonstrated a clinical benefit on combined aromatase and PIK3CA inhibitor therapy.

no approved therapies

variant present in combination

PIK3CA p.H1047R VAF **50%** RD **1,749** Tier II-C

For certain patients with hormone receptor (HR)-positive, HER2-negative breast cancer harboring mutated PIK3CA, a PIK3CA inhibitor in combination with an antiestrogen is approved and recommended (FDA, Health Canada, Swissmedic, TGA, NCCN). In a phase III clinical trial, patients with HR+, HER2- breast cancer harboring PIK3CA mutations treated with this drug combination demonstrated improved progression-free survival and better overall response rate compared to antiestrogen therapy alone; and in a phase II trial, 50.4% of patients, previously treated with CDK inhibitors, experienced clinical benefit without disease progression at six months on the combination therapy. In a phase III clinical trial of patients with HR+, HER2- breast cancer treated with a CDK4/6 inhibitor in combination with an antiestrogen, PIK3CA mutations were associated with similar clinical benefit as compared to wild-type PIK3CA. In a phase II clinical trial, patients with triple-receptor negative breast cancer harboring PIK3CA activating mutations were sensitive to an AKT inhibitor in combination with chemotherapy. In phase I clinical trials, patients with breast cancer harboring PIK3CA H1047R achieved clinical benefit on PI3K and PI3K/MTOR inhibitors. In a clinical case study, one patient with ER+, PR-, HER2- breast cancer harboring PIK3CA H1047R achieved clinical benefit on combination PIK3CA inhibitor and antiestrogen therapy. In a clinical study, PIK3CA H1047R was associated with worse overall survival in patients with breast cancer. Patients with solid tumors harboring activating PIK3CA mutations match inclusion criteria for clinical trials, such as trials with AKT inhibitors.

no approved therapies

Selected trials recruiting: **Female, age ≥ 18** within 10 miles of zip code - 1100 **Austria**

NCT04109066 Phase **3**

ESR1

Study of Nivolumab Versus Placebo in Participants With High-Risk Breast Cancer

EUDRACT2017-002961-23 Phase **3**

ESR1

A Multinational, Multicenter, Randomized, Phase 3 Study of Tesetaxel plus a Reduced Dose of Capecitabine versus Capecitabine Alone in Patients with HER2 Negative, Hormone Receptor Positive, Locally Advanced or Metastatic Breast Cancer Previously Treated with a Taxane

NCT03905343 Phase **3**

ESR1

Ribociclib-endocrine Combination Therapy Versus Chemotherapy as 1st Line in Visceral mBC

NCT03734029 Phase **3**

ESR1

Trastuzumab Deruxtecan (DS-8201a) Versus Investigator's Choice for HER2-low Breast Cancer That Has Spread or Cannot be Surgically Removed [DESTINY-Breast04]

NCT03701334 Phase **3**

ESR1

A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer

EUDRACT2019-002364-27 Phase **2**

ESR1

An open-label, two-arm, randomized, single-stage phase II study of ATezolizumab in combination with dual HER2 blockade plus epirubicin as NEoadjuvant therapy for HER2-positive early breast cancer

EUDRACT2016-004384-39 Phase **2**

BRCA1

EUDRACT2018-002990-24 Phase **3**

ESR1 D538G

Elacestrant Monotherapy vs. Standard of Care for the Treatment of Patients with ER+/HER2- Advanced Breast Cancer Following CDK4/6 Inhibitor Therapy: A Phase 3 Randomized, Open-Label, Active-Controlled, Multicenter Trial (EMERALD)

End of findings section

BRCA1 p.E111fs frameshift variant

Tier I-A

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
BRCA1 exon 6 truncating … BRCA1 pathogenic mutation	Loss of function	Chr:17 Pos:43104233 Change:C>CT	c.329dupA p.Glu111fs	ENST00000471181.6

Gene clinical summary
Somatic alterations in the BRCA1 tumor suppressor, such as small deletions that cause frameshift and loss of function, are found in cancers, including colorectal, lung, breast, and ovarian cancer (PMID: 27283171) (PMID: 27194814). Germline BRCA1 alterations cause hereditary breast and ovarian cancer (PMID: 27283171). BRCA1-deficient cells lack HR and are sensitive to platinum chemotherapies that block replication and approved poly ADP-ribose polymerase (PARP) inhibitors that block base excision repair. Combination therapies and other targets are under preclinical investigation to target other BRCA-deficient functions and secondary resistance, which may arise at a greater rate in repair-deficient cells (PMID: 28884397).

Variant group clinical summary
Variants in the BRCA1 gene are often of germline origin and may have implications for treatment decisions and clinical management for patients and family members; thus, germline testing should be considered in the appropriate clinical context (NCCN, ESMO). Germline pathogenic mutations in BRCA1 are associated with hereditary breast cancer (PMID: 27283171), (PMID: 29907802).

There are no therapies approved or recommended to treat patients with breast cancer harboring somatic BRCA mutations. However, the PARP inhibitors olaparib (FDA, EMA, Health Canada, Swissmedic, TGA, NCCN, ESMO, eviQ) and talazoparib (FDA, EMA, Health Canada, Swissmedic, TGA, NCCN, ESMO) are approved or recommended for certain HER2-negative breast cancer patients carrying germline pathogenic BRCA mutations.

Phase 3 clinical studies have reported improved progression-free survival (PFS) with olaparib (PMID: 28578601) and talazoparib (PMID: 30110579) treatment as compared to standard therapy in HER2-negative breast cancer patients carrying germline BRCA alterations, including patients with hormone receptor-positive and triple negative breast cancer. Subsequent analyses of these trials have reported that both olaparib (PMID: 31446213), (PMID: 30689707) and talazoparib (PMID: 31767793), (AACR 2020; abstr CT071) are associated with improved quality of life and patient reported outcomes, but do not significantly improve overall survival as compared to chemotherapy.

In a retrospective analysis, patients with either triple-receptor negative breast cancer or estrogen-receptor positive breast cancer harboring germline BRCA1/2 mutations experienced significantly higher pathological complete response rates as compared to patients without these mutations on neoadjuvant chemotherapy regimens (paclitaxel/nonpegylated liposomal doxorubicin/carboplatin or epirubicin/paclitaxel/cyclophosphamide) (PMID: 32163106).

Patients with breast cancer harboring BRCA germline or somatic mutations match inclusion criteria for clinical trials (NCT03575065), (NCT01506609), (NCT03499353).

Gene biological summary
BRCA1 is a protein with many binding partners and functions in DNA repair, cell cycle regulation, transcription, and apoptosis (PMID: 28884397). BRCA1 and PALB2 recruit BRCA2 and RAD51 to double strand breaks and stalled replication forks for repair by homologous recombination (HR) (PMID: 27530658). BRCA1 plays a role in G2/M, G2 accumulation, and S phase cell cycle checkpoints (PMID: 28884397) and appears to play a role in DNA replication at R-loops (PMID: 27530658). BRCA1 also forms a complex with BARD1 which has E3 ubiquitin ligase activity (PMID: 28884397). The important domains in BRCA1 include the RING domain (residues 24-65) and two BRCT domains (residues 1642-1736 and 1756-1855) (PMID: 28884397) (Uniprot.org).

Variant group functional summary

BRCA1 germline pathogenic mutations are deleterious mutations that have been classified by the ENIGMA Consortium as pathogenic (class 5) or likely pathogenic (class 4) (ClinVar) (ENIGMA BRCA1/2 Gene Variant Classification Criteria, June 2017). Additionally, this group includes truncating mutations that are predicted to have a loss of function due to the disruption or deletion of key functional domains, and are typically regarded as pathogenic (PMID: 20516115), (PMID: 16618730), (PMID: 29446198). Further analysis is warranted to determine the possible germline nature of these mutations if detected in the context of a somatic NGS test .

ESR1 p.D538G missense variant

Tier I-B

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
ESR1 activating mutation	Gain of function	Chr:6 Pos:152098791 Change:A>G	c.1613A>G p.Asp538Gly	ENST00000206249.7

Gene clinical summary
Alterations in ESR1 have been identified in cancers, including breast cancer. Gain-of-function mutations in the ligand binding domain commonly arise in ER+ breast cancer and lead to constitutive ER activation and acquired resistance to endocrine therapies (PMID: 28374222). Next-generation anti-estrogen therapies are under clinical and preclinical investigation for ESR1-mutated breast cancer (PMID: 26183887).

Variant clinical summary
In a combined analysis of two phase III trials, patients with estrogen-receptor positive breast cancer harboring ESR1 mutations demonstrated worse progression-free survival (2.4 vs 3.9 months; p=0.01) and one-year overall survival (62% vs 80%; p=0.04) on exemestane therapy (n=42) compared to fulvestrant therapy (n=73) (PMID: 32546646). In a phase II trial, fulvestrant treatment resulted in similar progression free survival in patients with ER positive breast cancer harboring ESR1 mutations and those who were ESR1 wild-type, and fulvestrant and pictilisib combination treatment did not improve progression free survival compared to fulvestrant alone (PMID: 27174596). In a phase I trial, 17 patients with estrogen-receptor positive breast cancer harboring ESR1 mutations achieved a partial response on the selective estrogen receptor degrader (SERD) elacestrant (J Clin Oncol 35, 2017 (suppl; abstr 1014)).

Patients with estrogen-receptor positive/HER2-receptor negative breast cancer harboring ESR1 activating mutations match inclusion criteria for clinical trials, such as trials with selective estrogen receptor degraders (NCT01823835).

In a retrospective analysis of a phase III trial, estrogen-receptor positive breast cancer patients harboring ESR1 D538G demonstrated improved progression-free survival when treated with a combination of exemestane and everolimus versus exemestane alone (5.8 vs 2.7 months) (PMID: 26681738).

In clinical studies of patients with estrogen-receptor positive breast cancer harboring ESR1 D538G, one achieved stable disease on pembrolizumab (PMID: 28945887), one progressed on letrozole and palbociclib (PMID: 28945887), and one progressed on exemestane (PMID: 28945887). ESR1 D538G was found as a secondary mutation in five patients with estrogen-receptor positive breast cancer after progression on anastrozole or letrozole (PMID: 25994408) (PMID: 28283903) (PMID: 28945887), and in two patients after progression on fulvestrant (PMID: 26243651) (PMID: 28283903). However, another patient showed a response on fulvestrant (PMID: 28945887).

In a retrospective analysis of metastatic breast cancer patients treated with aromatase inhibitors, ESR1 D538G (n=114) was associated with shorter overall survival (OS) (OS=25.99 months) and progression free survival (PFS) (PFS=2.69 months, HR=1.71) compared to wild-type ESR1 (OS=32.1 months and PFS=3.94) (PMID: 27532364). In a clinical study analyzing the ESR1 mutations in CTCs and matched cfDNA of a cohort of metastatic breast cancer patients who progressed after endocrine therapy, ESR1 D538G was detected in the CTCs and cfDNA of one patient with metastatic breast cancer who progressed on tamoxifen and two patients with metastatic breast cancer who progressed on fulvestrant (PMID: 29063679).

In preclinical studies, estrogen-receptor negative breast cancer cells transiently expressing ESR1 D538G demonstrated resistance to 4-hydroxy-tamoxifen and fulvestrant (PMID: 24185512) (PMID: 24217577).

Variant group clinical summary
In a combined analysis of two phase III trials, patients with estrogen-receptor positive breast cancer harboring ESR1 mutations demonstrated worse progression-free survival (2.4 vs 3.9 months; p=0.01) and one-year overall survival (62% vs 80%; p=0.04) on exemestane therapy (n=42) compared to fulvestrant therapy (n=73) (PMID: 32546646). In a phase II trial, fulvestrant treatment resulted in similar progression free survival in patients with estrogen-receptor positive breast cancer harboring ESR1 mutations and those who were ESR1 wild-type, and fulvestrant and pictilisib combination treatment did not improve progression free survival compared to fulvestrant alone (PMID: 27174596). In a phase I trial, 17 patients with estrogen-receptor positive breast cancer harboring ESR1 mutations achieved a partial response on the selective estrogen receptor degrader (SERD) elacestrant (J Clin Oncol 35, 2017 (suppl; abstr 1014)).

Patients with estrogen-receptor positive/HER2-receptor negative breast cancer harboring ESR1 activating mutations match inclusion criteria for clinical trials, such as trials with selective estrogen receptor degraders (NCT01823835).

Gene biological summary
ESR1 encodes estrogen receptor-α (ERα), which localizes to the nucleus upon estrogen ligand binding, where it recruits binding partners and acts as a transcription factor for genes involved in cell growth and differentiation, especially in mammary tissue. Important domains in ESR1 include the ligand binding domain (residues 302-595), the transcription activation function 1 domain (residues 1-180), the DNA-binding domain (residues 180-263), the hinge domain (residues 263-302), and the ligand-binding domain (residues 311-547) (Uniprot.org) (PMID: 26183887).

Variant functional summary
ESR1 D538G lies within the ligand-binding domain of ESR1 (PMID: 26183887). This mutation results in ligand-independent constitutive transcriptional activity, is transforming in culture, and promotes tumor formation in mouse models (PMID: 24185512), (PMID: 24185510), (PMID: 24217577), (PMID: 24398047), (PMID: 27472462), (PMID: 27986707).

Variant group functional summary
ESR1 activating mutations confer a gain of function on the ESR1 protein leading to constitutive estrogen receptor activation, as demonstrated via biochemical, in vitro, or in vivo assays (PMID: 28374222).

PIK3CA p.H1047R, **ESR1** p.D538G

Tier II-C

Variant combination clinical summary
In a clinical study, activating ESR1 mutations (D538G or Y537S, n=6) were associated with lack of clinical benefit in patients with HR+ breast cancer harboring PIK3CA activating mutations treated with alpelisib in combination with an aromatase inhibitor (letrozole or exemestane) (Nat Cancer 1, 382–393). However, in a phase Ib clinical trial, one patient with estrogen-receptor positive breast cancer harboring ESR1 D538G and a PIK3CA mutation demonstrated a clinical benefit when treated with the combination of letrozole and alpelisib (PMID: 27126994).

Variant combination functional summary
Activating mutations in PIK3CA confer a gain of function to the PIK3CA protein, which has been verified via biochemical, in vitro, or in vivo assays (PMID: 18079394).

ESR1 D538G lies within the ligand-binding domain of ESR1 (PMID: 26183887). This mutation results in ligand-independent constitutive transcriptional activity, is transforming in culture, and promotes tumor formation in mouse models (PMID: 24185512), (PMID: 24185510), (PMID: 24217577), (PMID: 24398047), (PMID: 27472462), (PMID: 27986707).

PIK3CA p.H1047R missense variant

Tier II-C

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
PIK3CA activating mutation PIK3CA codon 1047 mutat…	Gain of function	Chr:3 Pos:179234297 Change:A>G	c.3140A>G p.His1047Arg	ENST00000263967.3

Gene clinical summary
Oncogenic alterations in PIK3CA are found in cancers, including breast, colorectal, and liver cancer (PMID: 19305151). Amplifications and activating missense mutations in the kinase or helical domain typically affect either the catalytic activity of the protein or its regulation by binding partner p85, resulting in constitutive activation of the PI3K/AKT/MTOR pathway (PMID: 18079394). Approved and emerging PI3K, AKT, and MTOR inhibitors target the PI3K pathway (PMID: 27242542). Dual PIK3CA/MTOR inhibitors and combinations of PI3K and RAS pathway inhibitors are under clinical evaluation in PIK3CA-mutated cancers (PMID: 27915478).

Variant clinical summary
For certain patients with hormone receptor (HR)-positive, HER2-negative breast cancer harboring mutated PIK3CA, alpelisib in combination with fulvestrant is approved and recommended (FDA, Health Canada, Swissmedic, TGA, NCCN).

In a phase III clinical trial, patients with HR+, HER2- breast cancer harboring PIK3CA mutations treated with alpelisib and fulvestrant demonstrated improved progression-free survival and better overall response rate compared to fulvestrant alone (PMID: 31091374)(NCT02437318); and in a phase II trial, 50.4% (61/121) of patients, previously treated with CDK inhibitors, experienced clinical benefit without disease progression at six months on alpelisib and fulvestrant (J Clin Oncol 38(15): 1006) (NCT03056755). In a phase III clinical trial of patients with HR+, HER2- breast cancer treated with abemaciclib and fulvestrant, PIK3CA mutations (E542K, E545K, H1047L, or H1047R) were associated with similar clinical benefit as compared to wild-type PIK3CA (AACR 2020: Abstract 766). In a phase II trial, the AKT inhibitor ipatasertib in combination with the chemotherapy paclitaxel resulted in improved progression free survival (6.2 vs 4.9 months) compared to placebo in triple-receptor negative breast cancer patients harboring mutations in PIK3CA, AKT1, or PTEN (J Clin Oncol 35(15 Suppl): 1009-1009).

In a phase I trial, four patients with breast cancer harboring PIK3CA H1047R achieved a partial response on the PI3K inhibitor taselisib (PMID: 28331003). In another phase I trial, one patient with advanced hormone-receptor positive, HER2-receptor negative breast cancer achieved a partial response on the PI3K/MTOR inhibitor LY3023414 (J Clin Oncol 35(15 Suppl): 1064-1064). In another phase I trial, one patient with advanced hormone-receptor positive, HER2-receptor negative breast cancer harboring PIK3CA H1047R achieved a partial response on the PI3K/MTOR inhibitor LY3023414 (Journal of Clinical Oncology 35, no. 15_suppl (May 20 2017) 1064-1064). In a clinical case study, one patient with ER+, PR-, HER2- breast cancer harboring PIK3CA H1047R achieved clinical benefit on copanlisib and fulvestrant combination therapy (JCO Prec Oncology 4: 335-340).

In a study of 241 breast cancer patients, PIK3CA H1047R (n = 10) was associated with worse overall survival (P = 0.0083) compared to patients without PIK3CA mutations (PMID: 24471188).

Patients with solid tumors harboring activating PIK3CA mutations match inclusion criteria for clinical trials, such as trials with AKT inhibitors (NCT02761694).

Variant group clinical summary
In a phase III trial, patients with ER-positive, ERBB2-negative breast cancer harboring PIK3CA mutations demonstrated clinical benefit (improved progression-free survival and objective response rate) on taselisib in combination with fulvestrant (J Clin Oncol 36, 2018 (suppl; abstr LBA1006).

In a phase II trial, PIK3CA-mutant ER-positive, ERBB2-negative breast cancer patients had a higher overall response rate with the combination of taselisib and letrozole (41 of 73 patients responded) compared to those treated with letrozole and placebo (30 of 79 patients) (PMID: 31402321). In a phase II trial, the AKT inhibitor ipatasertib in combination with chemotherapy resulted in improved progression free survival (6.2 vs 4.9 months) compared to placebo in triple-receptor negative breast cancer patients harboring mutations in PIK3CA, AKT1, or PTEN (J Clin Oncol 35, 2017 (suppl; abstr 1009)). In a phase II trial, the AKT inhibitor capivasertib in combination with chemotherapy improved median progression-free survival (9.3 vs 3.7 months, HR=0.30, p=0.01) compared to placebo in patients with metastatic triple-negative breast cancer harboring PIK3CA, AKT1, and/or PTEN mutations (PMID: 31841354). In a phase II trial, 50.4% (61/121) of patients with ER-positive, ERBB2-negative breast cancer harboring PIK3CA mutations, previously treated with CDK inhibitors, experienced clinical benefit without disease progression at six months on alpelisib and fulvestrant combination therapy (J Clin Oncol 38(15): 1006) (NCT03056755).

In clinical trials, ERBB2-positive breast cancer patients harboring PIK3CA mutations demonstrated lower pathologic complete remission rate compared to those with wild-type PIK3CA after trastuzumab and lapatinib combination or single-agent therapy (PMID: 26245675)(PMID: 28177460).

Patients with solid tumors harboring activating PI3KCA mutations match inclusion criteria for clinical trials, such as trials with AKT inhibitors (NCT02761694).

Patients with solid tumors harboring PIK3CA codon 1047 mutations match inclusion criteria for clinical trials, such as trials with CDK4/6 and PI3K/MTOR inhibitors (NCT03065062).

Gene biological summary
PIK3CA encodes the p110α catalytic subunit of the heterodimeric PI3K complex (PMID: 18794884). Activated receptor tyrosine kinases recruit PI3K and activate the PI3K/AKT/MTOR pathway to regulate growth, proliferation, autophagy, and survival (PMID: 18767981). Important domains in PIK3CA include the helical domain (residues 525-696), the kinase domain (residues 697-1068), the adaptor-binding domain (residues 1-108), the RAS-binding domain (residues 191-291), and the C2 domain (residues 328-480) (PMID: 18079394) (Uniprot.org).

Variant functional summary
PIK3CA H1047R is a hotspot mutation that lies within the kinase domain of the PIK3CA protein (UniProt.org). This mutation results in increased phosphorylation of AKT and MEK1/2, growth factor-independent cell survival, and is transforming in cell culture (PMID: 26627007).

Variant group functional summary
Activating mutations in PIK3CA confer a gain of function to the PIK3CA protein, which has been verified via biochemical, in vitro, or in vivo assays (PMID: 18079394).

PIK3CA codon 1047 mutations are missense substitutions at residue 1047 of the PIK3CA protein. These hotspot mutations result in increased PIK3CA kinase activity and have transforming activity in cell culture (PMID: 15930273).

Variants of Unknown Significance

The variants listed here are not sufficiently characterized in the current literature and variant databases, and are therefore, currently, of uncertain or unknown clinical significance. They are reported here for future reference in the event they become clinically significant in light of additional supporting evidence.

TP53 p.E286G

Appendix

Genomic Regions Tested

We sequence all coding exons for each given transcript, plus approximately 10 basepairs of flanking non-coding DNA in each intron-exon junction. Unless specifically indicated, test results contain no information about other regions of the gene, such as regulatory domains or deep intronic regions. The genes on the panel: ABL1, AKT1, AKT2, AKT3, ALK, APC, AR, ATM, BAP1, BRAF, BRCA1, BRCA2, CCND1, CCNE1, CDH1, CDK12, CDK4, CDK6, CDKN1B, CDKN2A, CHEK2, CREBBP, CSF1R, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FANCA, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FLT1, FLT3, FLT4, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KDR, KEAP1, KIT, KRAS, MAP2K1, MAP2K2, MDM2, MDM4, MET, MLH1, MPL, MSH2, MSH6, MTOR, MYC, MYCN, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NPM1, NRAS, NTRK1, NTRK2, PALB2, PDGFRA, PDGFRB, PIK3CA, PIK3R1, PMS2, POLE, PPP2R1A, PTCH1, PTEN, PTPN11, RAF1, RB1, RET, ROS1, SMAD4, SMARCB1, SMO, SRC, STK11, TERT (including 454 bases upstream of translation start site), TP53, TSC1, TSC2, UGTA1A1, VHL.

LIMIT OF DETECTION: 5 percent variant allele fraction for single nucleotide variants (SNVs), small to medium sized multi-nucleotide variants (MNV) (less than 50bp).

Methodology

Genomic DNA is isolated from microscopically-guided dissection of tumor tissue and then enriched for the targeted regions of the tested genes. The variant status of the targeted genes is determined by massively parallel sequencing (next generation sequencing). The hg38 (GRCh38) reference sequence is used as a reference for identifying genetic variants.

Limitations

This test will not detect variants in areas outside the targeted genomic regions or below the assay's limit of detection. More complex structural variants, such as complex rearrangements, will not be detected. This test evaluates for variants in solid tumor tissue only. It cannot distinguish between somatic and germline variants.
For variants of potential germline origin, germline testing may be warranted. Consider seeking genetic counseling prior to such testing. In some cases, variants may not be identified due to technical limitations, especially when in the presence of known pseudogenes, homologous regions or regions of low mappability. Larger insertions or deletions (>50 basepairs) may not be detected.

Clinical Disclaimers

Interpretation of the test results is limited by the information that is currently available at the time. Treatment decisions are the responsibility of the physician. Results of this test must always be interpreted within the clinical context, such as the patient's conditions, patient and family history, physical examinations, information from other diagnostic tests and patient preferences.

The Inov Onco Panel was developed and its performance characteristics determined by Inov Labs.

NAVIFY® Mutation Profiler disclaimer

The information available in this report is obtained from third party sources (such as biomedical literature, medical guidelines, and publicly available data such as drug labels and clinical trials) and is subject to change over time based on future findings (including scientific and medical research).

NAVIFY® Mutation Profiler is not able to differentiate between germline and somatic variants. In general, variant interpretations are provided assuming the variants are of somatic origin.

3rd party attributions

A portion of the somatic gene variant annotations and related content have been provided by The Jackson Laboratory Clinical Knowledgebase (JAX-CKB™)

Clinical trial matching based on reported biomarkers are provided by MolecularMatch.

Tier definitions

Tier I-A: Approved therapy. Included in professional guidelines.

Tier I-B: Well-powered studies with consensus from experts in the field.

Tier II-C: Approved therapies for different tumor types or investigational therapies. Multiple small published studies with some consensus. Inclusion criteria for clinical trials.

Tier II-D: Limited clinical or preclinical studies.

Tier III (VUS): Variants of Unknown Clinical Significance.

Tier IV: Benign or likely benign variants (not included in the report, except for other biomarkers).

Software and content version numbers

NAVIFY® Mutation Profiler Version 2.0.0.7b4557e, Release date: 09/30/2020

NAVIFY® Therapy Matcher Version 2.0.0.7b4557e, Release date: 09/30/2020

Roche content Version 2.29.0, Release date: 08/18/2020

CIViC Version 01-july-2020, Release date: 07/01/2020

ClinVAR Version 20200727, Release date: 07/27/2020

COSMIC Version v91.r1, Release date: 04/07/2020

dbNSFP Version 4.0, Release date: 05/03/2019

gnomAD Version 2.1.1-VnV, Release date: 10/16/2019

TCGA Version 24.0.r2, Release date: 05/07/2020

Mitelman Version 15-apr-2020, Release date: 04/15/2020

dbVar Version 2020-06-07, Release date: 06/07/2020

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